

**UNITED STATES DISTRICT COURT  
EASTERN DISTRICT OF MISSOURI  
EASTERN DIVISION**

MONSANTO COMPANY and )  
MONSANTO TECHNOLOGY LLC, )  
 )  
Plaintiffs, )  
 )  
vs. )  
 )  
E.I. DUPONT DE NEMOURS AND ) Case No. 4:09-cv-686 ERW  
COMPANY and PIONEER HI-BRED )  
INTERNATIONAL, )  
INC., )  
 )  
Defendants. )

**DECLARATION OF DR. STEPHEN DELLAPORTA  
IN SUPPORT OF MONSANTO'S OPPOSITION TO  
DEFENDANTS' MOTION FOR SUMMARY JUDGMENT OF INVALIDITY**

1. I am a Professor of Molecular, Cellular, and Developmental Biology at Yale University. My background and expertise are set forth in my Expert Tutorial dated July 9, 2010, and my Expert Declaration dated January 15, 2010.

2. I have been informed that Defendants have filed a Motion for Summary Judgment alleging that certain claims of U.S. Patent No. RE 39,247 ("the '247 patent"), including asserted claims 115-119 and 122-125 (the "asserted claims"), have been improperly broadened compared to the scope of U.S. Patent No. 5,633,435 ("the '435 patent"). I have been asked to provide my expert scientific opinion in response to these allegations.

**Legal Background**

3. I understand that, as a legal matter, determining whether claims of the '247 reissue patent are broader than claims of the '435 patent involves a two-step process. First, I

understand that the claims of both patents must be interpreted, or “construed,” in order to determine their correct scope. Second, claims 115-119 and 122-125 of the ‘247 patent must be compared with the scope of the claims of the ‘435 patent. In order to demonstrate that these claims are broader than the scope of the ‘435 patent, I understand that Defendants bear the burden of proving, by clear and convincing evidence, that each of these claims could be infringed by a product that does not also infringe a claim of the ‘435 patent.

### **Claim Construction**

4. Claims 115-119 and 122-125 require a “glyphosate tolerant plant” or a “glyphosate tolerant plant cell” that comprises a DNA construct encoding an EPSPS enzyme having SEQ ID NO:70 (a predicted amino acid sequence listed in the ‘247 patent’s specification).

5. I understand that Defendants have interpreted the phrases “glyphosate tolerant plant” and “glyphosate tolerant plant cell” to require that the glyphosate tolerance of the claimed plants or plant cells must be “due to the production of a glyphosate-tolerant EPSPS enzyme which has the exact sequence of” SEQ ID NO:70. (Dkt. No. 243 at 40).

6. I understand that Monsanto has construed the phrase “glyphosate tolerant” plant or plant cells to require that the glyphosate tolerance be due at least to a functional DNA molecule *encoding* SEQ ID NO:70 that has been inserted into the plant’s genome. (Dkt. No. 259 at 33).

### **Comparison of the Scope of the Asserted Claims to Claim 4 of the ‘435 patent**

7. I understand that Defendants contend that the asserted claims to transgenic, “glyphosate tolerant” plants cells and plants are broader than Claim 4, because those plants and plant cells do not require (1) a heterologous promoter and (2) a functional 3’ non-translated

region. I disagree. It would be scientifically impossible for a plant or plant cell to be glyphosate tolerant due to DNA encoding SEQ ID NO:70 (or due to a specific protein with SEQ ID NO:70, according to Defendants' claim construction), unless the structural gene was associated with specific elements for a gene to function in a plant or plant cell.

### **Transgenes Capable of Functioning Inside Plant Cells**

8. In order for DNA encoding SEQ ID NO:70 to confer glyphosate tolerance in a plant cell, it is necessary for that DNA to be functional, or in the words of the '247 patent, "plant expressible." (Ex. 1, '247 patent, 5:30-35). Simply inserting the structural DNA containing the code for an enzyme with SEQ ID NO:70 into the chromosome of a plant cell is insufficient to confer glyphosate tolerance.

9. To confer glyphosate tolerance, the inserted DNA encoding SEQ ID NO:70 ultimately must cause the production of EPSPS enzymes. The EPSPS enzyme catalyzes the synthesis of the chemical EPSP, which is critical for the synthesis of certain amino acids, and thus, for the viability of the cell and plant. The EPSPS enzymes disclosed in the '247 patent – Class II EPSPS enzymes – are able to perform these essential catalytic functions in the presence of concentrations of glyphosate that inhibit the plant's natural EPSPS enzymes. (*Id.*, 9:21-34 (describing the characterization of Class II EPSPS enzymes and their novel catalytic activity, namely, a low  $K_m$  for the natural substrate PEP and a high  $K_i$  for glyphosate)). By this mechanism, Class II EPSPS enzymes confer glyphosate tolerance in transgenic plants.

10. A functional gene is required for the EPSPS enzymes to be produced, and hence, for glyphosate tolerance to be achieved in the plant or plant cell. The process leading to the synthesis of a Class II EPSPS enzyme contains several necessary steps. As I explained in my Expert Tutorial (provided in connection with Monsanto's opening brief on claim construction),

information encoded in the DNA must first be copied into a complementary RNA molecule in a process called “transcription,” which occurs inside the cell’s nucleus. (Dkt. No. 259-1 at ¶¶ 20, 23-24). Second, the RNA “transcript” must undergo processing steps inside the cell’s nucleus, including a step known as “polyadenylation,” which involves the addition of multiple adenosine nucleotides to the tail of the RNA molecule. (*Id.* at ¶¶ 20, 25). Outside the cell’s nucleus in the cytoplasm, the polyadenylated RNA molecule must be “translated” into a protein in an organelle called the “ribosome.” (*Id.* at ¶ 26).

11. The number of Class II EPSPS enzymes that are ultimately created in the cytoplasm is a major contributing factor to the glyphosate tolerance of the cell. The number of enzymes created is directly dependent on the number of times DNA is transcribed into RNA, and how often the RNA is translated into a protein. Simply put, if the transgenic plant or plant cell is not capable of transcribing and processing enough structural DNA encoding SEQ ID NO:70, and translating enough of the EPSPS enzymes, then the plant cell will not exhibit sufficient glyphosate tolerance due to that gene.

**Claims 115-119 and 122-125 Necessarily Require a Functional, Heterologous Promoter.**

12. Scientifically, it would be impossible to impart glyphosate tolerance to a plant or plant cell using a structural DNA sequence encoding SEQ ID NO:70, if that structural DNA sequence lacked a promoter capable of functioning inside a plant cell to cause transcription.

13. As I have explained in my Expert Tutorial, promoters are DNA sequences that bind transcription factors, and recruit the enzyme RNA polymerase that is required to transcribe RNA. (*Id.*, at ¶¶ 23-24). Promoters define where transcription begins, the level of transcription, and the template strand of DNA copied by the RNA polymerase enzyme. Without a promoter, a

structural DNA sequence would not be transcribed in the plant cell, and therefore, unable to produce *any* EPSPS enzyme that could confer glyphosate tolerance.

14. By definition, for any EPSPS gene to cause glyphosate tolerance in a plant or plant cell, it *must* have a promoter that functions in the plant or plant cell. Therefore, I cannot conceive of any plant that is glyphosate tolerant due to DNA encoding an EPSPS enzyme having SEQ ID NO:70 (according to Monsanto's claim construction), lacking a promoter that functions in plant cells. Nor can I conceive of any plant that is glyphosate tolerant due to the production of an enzyme having exactly SEQ ID NO:70 (according to Defendants' claim construction), lacking a promoter that functions in plant cells.

15. Moreover, in order to function in plant cells, the promoter must be "heterologous with respect to the structural DNA sequence." I understand that both parties have interpreted this phrase to mean that the promoter cannot come from the same gene as the structural DNA sequence. (Defs' Claim Constr. Br., Dkt. No. 243, at 19; Monsanto's Claim Constr. Br., Dkt. No. 259, at 27). Thus, the promoter cannot come from the CP4 EPSPS gene, but *can* come from any other gene. As I discuss below, the native promoter of the CP4 EPSPS gene – the only homologous promoter – simply will not work to confer glyphosate tolerance in plant cells.

16. With rare exceptions, bacterial promoters will not function in plant cells. Over the course of over a billion years of evolution, DNA sequences that function as promoters in plants and bacteria have diverged. The internal machinery in plant cells necessary for transcription (such as the plant RNA polymerase enzymes and other transcription factors) cannot effectively recognize bacterial promoters. For example, bacterial promoters are characterized by conserved sequences (motifs) found ten base pairs (bp) upstream (-10) from the start point of

transcription and a second motif found 35 bp upstream (-35).<sup>1</sup> The distance between these motifs, conserved in over 90% of bacterial promoters, is essential for stable binding of the bacterial RNA polymerase and other bacterial transcription factors which interact with these regions. In contrast, eukaryotic promoters, such as those found in plants and animals, are highly complex, containing a conserved “TATA box” motif at -30, a “CAAT box” at -75, and a “GC box” at -90.<sup>2</sup> Further upstream, additional cis-acting elements may be required for high levels of transcription and tissue-specific gene regulation. At least 40 different proteins assemble around the TATA box to form a competent initiation complex, demonstrating the extreme complexity of eukaryotic promoters.

17. Weak transcription of certain plant promoters, including the CaMV 35S promoter, has been observed when tested in bacteria, most likely because the requirements for bacterial promoters are much less complex than plant promoters. The reverse situation, *i.e. bacterial* promoters functioning in plants, however, has not been generally reported in the scientific literature. The rare exception involves special promoters in the T-DNA genes of *Agrobacterium*, the very few promoters known to be active in plants. EPSPS structural genes, however, are found within operons (functional units containing a cluster of related genes that are transcribed from a common bacterial promoter) whose expression is controlled by bacterial promoters.

18. A homologous promoter from the EPSPS gene of *Agrobacterium* will not work to confer glyphosate tolerance in plant cells. Thus, although the inventors isolated the Class II EPSPS structural coding sequence from the CP4 bacteria, the inventors did not – and could not – use the CP4 *promoter* to cause transcription of DNA encoding SEQ ID NO:70 in a plant cell. All of the examples of gene constructs in the ‘247 patent use promoters from different genes

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<sup>1</sup> These positions and the exact sequence motif can vary slightly among promoters.

<sup>2</sup> These positions and the exact sequence motif can vary slightly among promoters.

other than the CP4 EPSPS gene. (See, e.g., Ex. 1 at 7:47-67, 8:28-36) (identifying promoters that are all heterologous to CP4 EPSPS coding sequence); *id.* at Figs. 13-17 (transformation vectors all containing CP4 EPSPS and heterologous promoters)).

19. In my opinion, any transgenic plant that is glyphosate tolerant due to a structural DNA sequence encoding SEQ ID NO:70, necessarily must contain a “heterologous” promoter that comes from a different gene than the EPSPS coding sequence of CP4 bacteria. A “homologous” promoter coming from the CP4 bacterial gene would not function in plants to cause any significant degree of transcription of the structural DNA encoding SEQ ID NO:70, and it would be impossible for that promoter to transcribe sufficient quantities of structural DNA to result in glyphosate tolerance.

**Claims 115-119 and 122-125 Necessarily Require a Functional 3' Non-Translated Region**

20. Likewise, it would be impossible for DNA encoding an EPSPS enzyme having SEQ ID NO:70 to confer glyphosate tolerance in a plant or plant cell, unless that DNA had a 3' non-translated region (“3' NTR”) capable of signaling polyadenylation of the RNA transcript.

21. Once the enzyme RNA polymerase has reached the end of the gene, it encounters specific sequences (a polyadenylation signal) that, after being transcribed into RNA, trigger the addition of a stretch of polyadenyl nucleotides to the 3' end of RNA. The poly(A) tail is added after transcription, and is required for the nuclear export, translation and stability of mRNA.

22. Unlike polyadenylated RNA that is rapidly exported to cytoplasm for protein translation, unpolyadenylated RNA is known to accumulate in the nucleus, where it cannot be translated. (E.g., Ex. 7, Huang and Carmichael, 1996). Improperly terminated, unpolyadenylated mRNA transcribed from a plant transgene has been shown to be subject to degradation and gene silencing. (Ex. 8, Luo and Chen, 2007). Furthermore, translational

efficiency of unpolyadenylated mRNA is low. (Ex. 9, Munroe and Jacobson, 1990). These observations, and many others, provide overwhelming scientific evidence that polyadenylation is essential for gene expression.

23. The function of the 3' NTR described in claim 4 is to provide for sequences required for 3' polyadenylation. Thus, the 3' NTR is an essential component for a "glyphosate-tolerant" plant or plant cell defined in claims 115 and 116. Without a 3' NTR, a specific poly(A) signal would be missing from RNA. Without RNA stability, transport and translation conferred by the poly(A) tail, achieving a glyphosate tolerant plant or plant cell would be impossible.

24. Thus, I cannot conceive of any plant that is glyphosate tolerant due to structural DNA encoding an EPSPS enzyme containing SEQ ID NO:70, which lacks a 3' NTR capable of causing polyadenylation.

**DNA Encoding SEQ ID NO:70 is Contained Within the Sequence Motifs Described in Claim 4.**

25. It is my understanding that Defendants do not assert that the DNA recited in claims 115-119 and 122-125 is outside of the broad genus of compounds set forth in claim 4 of the '435 patent. Nevertheless, I have been asked to compare SEQ ID NO:70 with the sequence motifs described in Claim 4 of the '435 patent, to determine whether DNA encoding SEQ ID NO:70, as stated in the asserted claims of the '247 patent, falls within the genus of compounds claimed in Claim 4 of the '435 patent. I confirm that it does.

26. DNA encoding SEQ ID NO: 70 clearly falls within the broad sequence listing stated in Claim 4 of the '435 patent. The specific motifs defined in Claim 4 are listed in the left-hand column of Table 1, below. The sequence present in SEQ ID NO: 70 that matches these motifs are shown in the right column, together with their positions in the amino acid sequence of SEQ ID NO: 70.

| <i>Motif</i>                            | <i>SeqID 70 Match</i>             |
|---|-----------------------------------|
| -R-X <sub>1</sub> -H-X <sub>2</sub> -E- | -R-D-H-T-E at position 200...204  |
| -G-D-K-X <sub>3</sub> -                 | -G-D-K-S- at position 26...29     |
| -S-A-Q-X <sub>4</sub> -K-               | -S-A-Q-V-K- at position 173...177 |
| -N-X <sub>5</sub> -T-R-                 | -N-P-T-R- at position 271...274   |

whereby, X<sub>1</sub> is G, S, T, C, Y, N, Q, D or E; X<sub>2</sub> is S or T; X<sub>3</sub> is S or T; X<sub>4</sub> is A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y or V; and X<sub>5</sub> is A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y or V.

27. From this analysis, I conclude that DNA encoding an EPSPS enzyme having SEQ ID NO:70 meets the criteria for a structural DNA sequence encoding a Class II EPSPS enzyme, as described in Claim 4 of the '435 patent.

I hereby declare, under penalty of perjury, that the foregoing is true and correct.

Executed this 12th day of July, 2010.

By: Stephen L. Dellaporta  
Stephen L. Dellaporta, Ph.D

Respectfully submitted,

HUSCH BLACKWELL SANDERS LLP

By: /s/ Joseph P. Conran.

Joseph P. Conran, E.D.Mo. # 6455  
joe.conran@huschblackwell.com  
Omri E. Praiss, E.D.Mo. # 35002  
omri.praiss@huschblackwell.com  
Greg G. Gutzler, E.D.Mo. # 84923  
greg.gutzler@huschblackwell.com  
Tamara M. Spicer, E.D.Mo. # 122214  
tamara.spicer@huschblackwell.com  
Steven M. Berezney, E.D.Mo. # 499707  
steve.berezney@huschblackwell.com  
190 Carondelet Plaza, Suite 600  
St. Louis, MO 63105  
(314) 480-1500 – telephone  
(314) 480-1505 – facsimile

MCDERMOTT WILL & EMERY

Steven G. Spears  
sspears@mwe.com  
1000 Louisiana Street  
Suite 3900  
Houston, TX 77002-5005  
(713) 653-1700 – telephone  
(713) 739-7592 – facsimile

COVINGTON & BURLING LLP

Kurt G. Calia  
kcalia@cov.com  
1201 Pennsylvania Avenue, NW  
Washington, DC 20004-2401  
(202) 662-6000 – telephone  
(202) 662-6291 – facsimile

WINSTON & STRAWN LLP  
Dan K. Webb  
dwebb@winston.com  
Todd J. Ehlman  
tehlman@winston.com  
35 W. Wacker Drive, Suite 4200  
Chicago, IL 60601  
(312) 558-5600 – phone  
(312) 558-5700 – facsimile

John J. Rosenthal  
jrosenthal@winston.com  
Matthew Campbell  
macampbell@winston.com  
1700 K Street, N.W.  
Washington, DC 20006  
(202) 282-5000 – phone  
(202) 282-5100 – facsimile

ARNOLD & PORTER LLP  
Anthony J. Franze  
anthony.franze@aporter.com  
555 Twelfth Street, N.W.  
Washington, DC 20004  
(202) 942-5000 – telephone  
(202) 942-5999 – facsimile

*Attorneys for Plaintiff Monsanto Company and  
Monsanto Technology LLC*

**CERTIFICATE OF SERVICE**

The undersigned hereby certifies that on the 12th day of July, 2010, the foregoing was filed electronically with the Clerk of the Court for the United States District Court Eastern District of Missouri, Eastern Division, and was served by operation of that Court's electronic filing system, upon the following:

Andrew Rothschild, Esq.  
C. David Goerisch, Esq.  
Lewis, Rice & Fingersh, L.C.  
600 Washington, Suite 2500  
St. Louis, MO 63102

Leora Ben-Ami, Esq.  
Thomas F. Fleming, Esq.  
Christopher T. Jagoe, Esq.  
Howard S. Suh, Esq.  
Jeanna Wacker, Esq.  
Kaye Scholer LLP  
425 Park Avenue  
New York, NY 10022

Donald L. Flexner, Esq.  
Hershel Wancjer, Esq.  
Cynthia Christian, Esq.  
Robert M. Cooper, Esq.  
Boies, Schiller & Flexner LLP  
575 Lexington Avenue, 7th Fl.  
New York, NY 10022

James P. Denvir, Esq.  
Amy J. Mauser, Esq.  
Boies, Schiller & Flexner LLP  
5301 Wisconsin Avenue, N.W.  
Washington, D.C. 20015

*Attorneys for Defendants*

/s/ Joseph P. Conran .